

REMARKS

The undersigned thanks Examiner Wilder for the courtesies extended during the telephone interview of April 8, 2008. During the interview, the Examiner provided excellent suggestions to the undersigned to overcome the pending obviousness rejections. In particular, the Examiner said that the unexpected results of the apparatus of the claimed invention, namely that the claimed apparatus and method are the first for Raman detection of nucleotides at the *single nucleotide* level. The Examiner recognized that prior to this invention there was no reported apparatus or method that could detect nucleotides at the single nucleotide level by Raman. The Examiner suggested that particularly in light of the recent Supreme Court decision in *KSR v. Teleflex*, 550 U.S. ___, 127 S. Ct. 1727 (2007), it would be particularly useful to include a showing of unexpected results to overcome the obviousness rejections. This Amendment has been prepared with the advice of the Examiner in mind.

Claim Rejections - 35 USC § 112

Claims 26-34 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed.

The Examiner states that the term “adapted” is ambiguous. This term has been replaced with “positioned” as “Applicant is referring to the position of the electrodes” as understood by the Examiner in paragraph 4(a), line 4, of the Action.

Claim Rejections - 35 USC § 103

Claims 26-34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Shipwash in view of Shipway et al (citation made of record in the prior Office actions) and further in view of Williams et al (2002/0039738, effective filing date April 24, 2001).

This rejection is respectfully traversed.

Apparatus claim 26 has been amended to clearly recite “a hot spot having a three-dimensional porous structure, the hot spot being stationary within the second channel and comprising a plurality of cross-linked nanoparticle aggregates affixed within the hot spot within the second channel, wherein the hot spot enhances a Raman signal of the single nucleotide.” A “hot spot having three-dimensional porous structure” is disclosed in paragraph [0025] and Figure 1 of the specification. Please note that the hot spot 111 of Figure 1 is stationary and has a three-dimensional porous structure. In particular, Figure 1 shows that the stationary hot spot 111 comprises a plurality of cross-linked nanoparticle aggregates (shown by ovals) affixed within the hot spot 111 within the second channel 103. Also, note that the stationary hot spot 111 of Figure 1 is porous as fluid (shown by straight line) flows through the stationary hot spot 111. Paragraph [0025] also discloses: “Nucleotides 110 associated with a ‘hot spot’ produce an enhanced Raman signal that may be detected using a detection unit comprising, for example, a laser 106 and CCD camera 107.” Claim 26 recites “a Raman detector operably coupled to the second channel to detect the single nucleotide” is supported by paragraph [0094] states that “the detector 107 may be capable of detecting and identifying single nucleotides.”

Claim 26 recites “[a]n apparatus for detecting a single nucleotide by Raman spectroscopy” and furthermore recites structural features of such an apparatus. Prior to this invention, there was no apparatus that was capable of detecting a single nucleotide by Raman. Shipwash fails to disclose

a Raman apparatus capable of detecting a single nucleotide. Instead, Shipwash discloses a fluorescence spectroscopy method and apparatus for detecting a single fluorescent labeled nucleotide.

Shipway has been cited for teaching a “charged nanoparticle and an oppositely charged ‘crosslinker’” (see page 4, lines 7-8 from the bottom, of the Action). Shipway discloses nanoparticle arrays on surfaces. See title of Shipway, “*Nanoparticle Arrays on Surfaces for Electronic, Optical, and Sensor Applications.*” Williams has been cited for teaching a microfluidic system having a pair of electrodes for control of the motion of nucleotides. However, Shipway and Williams also fail to disclose an apparatus for detecting a single nucleotide by Raman spectroscopy having “a Raman detector operably coupled to the second channel *to detect the single nucleotide,*” as recited in claim 26. Thus, the cited references as a whole fail to teach or suggest the claimed Raman apparatus having the claimed Raman detector for detecting *a single nucleotide* by Raman spectroscopy.

Claim 38 recites “electrodes positioned to create a field to guide the single nucleotide from the first channel into the second channel such that the single nucleotide passes through the hot spot.” On page 5, lines 10-12, of the Action, the Examiner has acknowledged that “Shipwash in view of Shipway et al do not expressly teach wherein the electrode is adapted to create a field to guide nucleotides from the first channel into the second channel” and cites Williams to fill this gap. However, the “electrodes [of Williams are not] positioned to create a field to guide the single nucleotide from the first channel into the second channel such that the single nucleotide passes through the hot spot.”

Furthermore, a careful review of Shipwash shows that the apparatus of Shipwash such as that shown in Figure 14 does *not* need any electrodes to guide nucleotides from the first channel into

the second channel as the first channel is bent into the second channel such that the only direction which the flow from the first channel can proceed is through the bent into the second channel. In short, persons of ordinary skill in the art would not have been motivated to modify the apparatus of Shipwash by the inclusion of the electrodes of Williams that are configured to create a field to guide nucleotides from the first channel into the second channel. “Rejections on obviousness grounds cannot be sustained by *mere conclusory statements*; instead, there *must* be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”. *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350, slip op. at 11 (U.S. April 30, 2007)(citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)(emphasis added)).

Unexpected Results

Even assuming that the cited prior art establishes a *prima facie* case of obviousness, which Applicants respectfully deny, the Examiner is requested to consider the ***unexpected results*** of the claimed invention. The unexpected results are at least shown in paragraphs [0094] and [0103] of the specification. In particular, the present invention is “the first report of Raman detection of nucleotides at the single nucleotide level.” See paragraph [0103]. “Table 1 shows exemplary detection limits for various analytes of interest.” See paragraph [0102]. In particular, Table 1 shows Applicants were able to detect a *single nucleotide* (dAMP) by Raman spectroscopy by the apparatus and method of the claimed invention. This result is truly remarkable and unexpected. Prior to this invention, nobody had been able to detect a *single nucleotide* by Raman spectroscopy.

During the interview, the Examiner suggested that Applicants should clarify the unexpected results of this invention. As explained in *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), when the expected results are present in the application, there is no need to submit a separate declaration under 37 CFR 1.32. In the present case, as “applicant demonstrates

substantially improved results, as Soni did ..., and states [in paragraph 0103 of the specification] that the results were [first and] unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary.” 54 F.3d at 751, 34 USPQ2d at 1688.

During the interview the Examiner said that Applicants should recite the unexpected results in claim 26; thus, claim 26 recites an “apparatus for detecting a single nucleotide by Raman spectroscopy” in the preamble and “a Raman detector operably coupled to the second channel *to detect the single nucleotide*” within the claim after the preamble. In light of the amendments of claim 26 and showing of unexpected results as suggested by the Examiner, Applicants respectfully submit that the present application should now be in a condition for allowance.

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Respectfully submitted,

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